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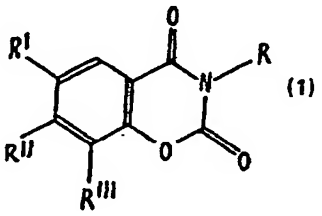
(54) **New derivatives of 1,3-benzoxazine-2,4-dione, their preparation and their application as medicaments**

(57) The invention concerns 1,3-benzoxazine-2, 4-dione derivatives of the formula



(1)

In which R represents an alkyl radical, an *ortho*-phenoxy-phenyl, *ortho*-thiophenoxy-phenyl, a benzyl, furfuryl or 2-pyridyl group; R′ represents a hydrogen, chlorine, or bromine atom or a methoxy radical; R″ represents a hydrogen or chlorine atom or a methyl radical; and R‴ represents a hydrogen, chlorine or bromine atom. R preferably represents a C_1 to C_4 alkyl radical. The derivatives of the invention have pharmacological (e.g. analgesic and anti-inflammatory) activity and may be administered in tablet, capsule, suppository and the like forms. Methods for the preparation of these derivatives are disclosed.

Certain of the chemical formulae appearing in the printed specification were submitted in formal form after the date of filing.

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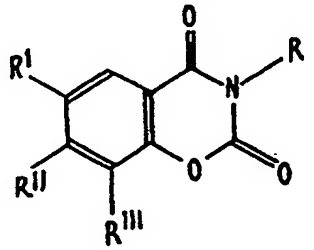
SPECIFICATION

New derivatives of 1,3-benzoxazine-2,4-dione, their preparation and their application as medicaments

The present invention provides new derivatives of 1,3-benzoxazine-2, 4-dione, their preparation and their application as medicaments.

The new derivatives of the present invention, have with the general formula I

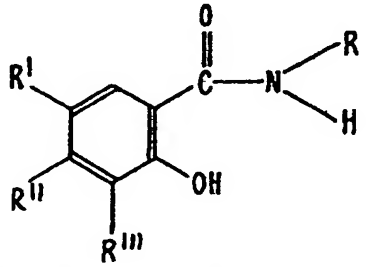


(I)

in which R represents an alkyl radical, especially a lower alkyl radical preferably with C_1 to C_4, an ortho-phenoxy-phenyl, ortho-thiophenoxy-phenyl, a benzyl, furfuryl or a 2-pyridyl group;
R' represents a hydrogen, chlorine, or bromine atom or a methoxyl radical;
R'' represents a hydrogen or chlorine atom or a methyl radial; and
R''' represents a hydrogen, chlorine or bromine atom.

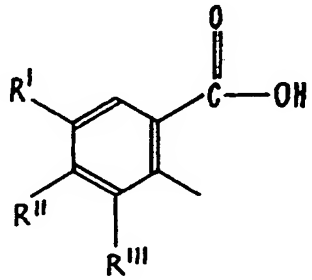
The derivatives of general formula I have proved to possess valuable pharmacological properties. The present invention therefore also relates to the application of these compounds as medicaments as well as to pharmaceutical compositions containing them as active ingredient.

The present invention also relates to the preparation of derivatives of general formula I. According to the invention, these derivatives of general formula I are obtained:
a) by reaction of a derivative of salicylamide of general formula II



(II)

in which R, R', R'' and R'''have the meanings indicated in connection with general formula I, with ethyl chlorocarbonate; or
b) by reaction of a derivative of salicylic acid of general formula III



(III)

in which R', R'' and R''' have the meaning indicated in connection with general formula I, with an isocyanate of general formula IV

$$O=C=N-R \qquad (IV)$$

in which R has the meaning given in connection with general formula I.

By way of simple non-limiting examples, the preparation of a few derivatives of general formula I will hereinafter be described in more detail.

EXAMPLE 1

Preparation of 6-chloro-3-methyl-1, 3-benzoxazine-2, 4-dione

37 ml (0.375 mole) of ethyl chlorocarbonate is added slowly (1/2 hour) to a solution of 18.6 g (0.1 mole) of 5-chloro-N-methylsalicylamide in pyridine. It is allowed to reflux for 7 hours, allowed to cool, is diluted with water, filtered and washed with distilled water. It is recrystallised from chloroform, washed with methanol at 5°C and 6-chloro-3-methyl-1, 3-benzoxazine-2, 4-dione with melting point 151—153°C (see Table I) is obtained.

EXAMPLE 2

Preparation of 6-bromo-3-methyl-1, 3-benzoxazine-2, 4-dione

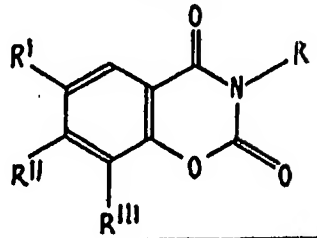
7.5 ml (0.12 mole) of methyl isocyanate and 5 ml of triethylamine are added to a solution of 21.7 g (0.1 mole) of 5-bromosalicylic acid in 150 ml of benzene.

The mixture is stirred for 1 hour at ambient temperature and then allowed to reflux for 6 hours. It is evaporated to dryness, recrystallised from methanol and 6-bromo-3-methyl-1,3-benzoxazine-2,4-dione with melting point 186°C (see Table I) is obtained.

EXAMPLES 3 TO 17

By operating as described in Examples 1 and 2 various derivatives were obtained, a number of the physio-chemical constants of which, such as the crystallisation solvents, the melting points and the characteristic bands of the infra-red spectrum are indicated in Table I hereinafter.

TABLE I



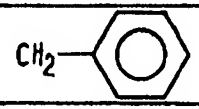
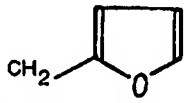
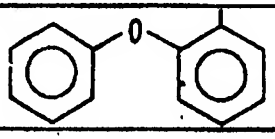
Ex. No.	R	R'	R''	R'''	Melting Point	Crystallisation Solvent	Yield %	IR (cm^{-1})	ANALYSIS					
										C	H	Cl	Br	N
1	CH_3	Cl	H	H	151–3	$CHCl_3$	93	1300, 1350 1690, 1770	Calc. Found	51,12 51,20	2,86 2,79	16,76 16,70	–	6,63 6,57
2	CH_3	Br	H	H	188	CH_3OH	19	1300, 1350 1690, 1750	Calc. Found	42,23 42,15	2,36 2,41	–	31,14 31,27	5,47 5,32
3	$CH_2CH_2CH_3$	Cl	H	H	118	CH_3OH	52	1340 1700, 1770	Calc. Found	55,17 55,25	4,21 4,15	14,80 14,73	–	5,85 5,97
4	$CH(CH_3)_2$	Cl –	H	H	167–9	CH_3OH	24	1330 1700, 1770	Calc. Found	55,17 55,08	4,21 4,32	14,80 14,86	–	5,85 5,80
5	$CH_2CH_2CH_2CH_3$	Cl	H	H	103	CH_3CH_2OH	12	1300 1700, 1770	Calc. Found	56,87 56,79	4,75 4,81	14,00 13,92	–	5,52 5,46
6	$(CH_2)_{15}CH_3$	Cl	H	H	97	CH_3COCH_3	67	1350 1700, 1770	Calc. Found	68,31 68,42	8,60 8,56	8,40 8,35	–	3,32 3,25
7		Cl	H	H	152–5	CH_3OH	42	1340 1710, 1770	Calc. Found	62,60 62.55	3,51 3,57	12,33 12,28	–	4,87 4,97
8		Cl	H	H	178–80	EtOH/Me_2CO	46	1320 1700, 1770	Calc. Found	56,27 56,14	2,90 2,87	12,77 12,69	–	5,05 4,98
9		Cl	H	H	167	EtOH	70	1360 1710, 1770	Calc. Found	65,73 65,81	3,30 3,34	9,70 9,77	–	3,83 3,95

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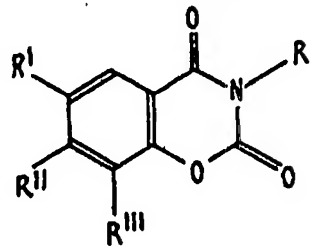
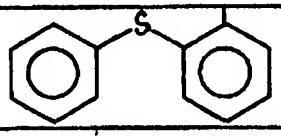
TABLE I (continued)



Ex. No.	R	R′	R″	R‴	Melting Point	Crystallisation Solvent	Yield %	IR (cm^{-1})	ANALYSIS					
										C	H	Cl	Br	N
10		Cl	H	H	150	EtOH	98	1360 1710, 1770	Calc. Found	62,90 63,02	3,17 3,09	9,29 9,34	–	3,67 3,80
11	CH_3	H	Cl	H	192–4	CH_3OH	10	1300, 1360 1690, 1760	Calc. Found	51,11 50,98	2,86 2,93	16,78 16,89	–	6,62 6,63
12	CH_2CH_3	Cl	H	H	120–2	$C Cl_4$	51	1340, 1350 1700, 1770	Calc. Found	53,27 53,15	3,58 3,63	15,72 15,74	–	6,22 6,15
13	CH_3	Cl	H	Cl	159–63	AcoEt	6	1300, 1360 1690, 1770	Calc. Found	43,94 44,05	2,05 1,98	28,82 28,91	–	5,69 5,75
14	$CH_2CH_2CH_2CH_3$	Cl	H	Cl	106–8	CH_3OH	46	1340 1700, 1770	Calc. Found	50,00 49,87	3,85 3,91	24,61 24,57	–	4,86 4,79
15	$CH_2CH_2CH_2CH_3$	Br	H	Br	139	EtOH	38	1350 1690, 1770	Calc. Found	38,23 38,32	2,94 3,01	–	42,39 42,53	3,72 3,77
16	CH_3	CH_3O	H	H	138–40	CH_3OH/H_2O	23	1300, 1355 1690, 1760	Calc. Found	58,02 57,91	4,38 4,42	–	–	6,77 6,85
17	CH_3	H	CH_3	H	164	CH_3OH	12	1300, 1370 1690, 1760	Calc. Found	62,89 62,97	4,75 4,70	–	–	7,33 7,40

Analgesic activity

The analgesic activity of the derivatives of general formula I has been determined using male mice of weight between 20 and 25 g. The product to be tested is administered orally in suspension in 5 % gum arabic by means of an oesophageal probe. The volume of the solution administered is 25 ml/kg and the concentration of the tested product is changed according to the dose administered.

Pain is caused in the animals by an intraperitoneal injection of 0.2 ml/20g solution of acetylcholine bromide with a concentration of 0.32 ml/ml. Five minutes before the administration of the tested product, the acetylcholine is injected into a batch of 5 mice. The product to be tested is then administered and the injection of acetylcholine is administered again after 20, 40, 80, 120 and 160 minutes. The number of contortions per injection of acetylcholine is always counted for 5 minutes.

The analgesic activity is calculated by means of the following formula:

$$It = 100 - (Nt/No).100 = 100\,(1-Nt/No)$$

where

It = inhibition of the pain after t minutes

No = number of contortions before the administration of the product

Nt = number of contortions after t minutes from the administration of the product.

Several doses of each product are administered so that the fifty per cent analgesic dose (AD—50) can be determined.

With each of these doses It is calculated for times of 20, 40, 80, 120 and 160 minutes. The mean of these five values of It for each dose is taken as the analgesic effect. The analgesic effects are represented graphically as a function of the logarithm of the corresponding dose.

From this curve the analgesic dose fifty, that is to say, the dose which produces a fifty per cent analgesic effect, is obtained.

By way of example, the results obtained for a few derivatives of formula I according to the invention have been indicated in Table II hereinafter.

Acute toxicity

The acute toxicity is determined orally with mice of 20 to 25 g weight, by using batches of 6 animals. Several doses in geometric progression are administered. The time of observation is 72 hours. The fifty per cent lethal dose (LD—50) is calculated graphically by means of logarithmic-probabilistic paper.

By way of example, the results obtained for a few derivatives of formula I according to the invention are indicated in Table II hereinafter.

TABLE II

Example No.	Derivative:	Doses in mg/kg	
		AD—50	LD—50
1	6-chloro-3-methyl-1,3-benzoxazine-2,4-dione	30	233
2	6-bromo-3-methyl-1,3-benzoxazine-2,4-dione	90	717
3	6-chloro-3-propyl-1,3-benzoxazine-2,4-dione	240	>650
8	6-chloro-3-furfuryl-1,3-benzoxazine-2,4-dione	280	>550
9	6-chloro-3-(O-phenoxyphenyl)-1,3-benzoxazine-2,4-dione	675	>750
10	6-chloro-3-(O-thiophenoxy-phenyl)-1,3-benzoxazine-2,4-dione	650	>1500
12	6-chloro-3-ethyl-1,3-benzoxazine-2,4-dione	172	>250

Anti-inflammatory activity

The anti-inflammatory activity in the male rat of Sprague-Dawley stock is determined. An oedema is caused in the paw by subplantar injection of a 1 % solution of carrageenin. The volume of the paw is measured before the oral administration of the product after two and five hours with a plethysmometer. The anti-inflammatory activity is calculated with respect to a reference batch. By way of example, the results obtained for the derivative of example I are indictated in Table III.

TABLE III

Example	Derivative	Dose (mg/kg)	Anti-Inflammatory Activity	
			2 hours	5 hours
1	6-chloro-3-methyl-1,3-benzoxazine-2,4-dione	100	26%	30%

Taking into account their good pharmacodynamic properties, the derivatives of general formula I are hence capable of being used as veterinary and/or human medicine, as analgesic, antipyretic and anti-inflammatory agents.

Pharmaceutical compositions which contain, according to the invention, besides an acceptable pharmaceutical support, at least one derivative of general formula I have a very large field of therapeutic application and can be utilised especially in traumatology, surgery, rheumatology, odonstostomatology, oto-rhino-laryngology, pneumology, cardiology, gynaecology and urology. These pharmaceutical compositions will be, for example, utilised for the treatment of various manifestations of pain, headaches, migraines, toothache, neuralgias, menstrual pains, inflammatory rheumatisms, arthritis pains, feverish states, colds, influenzas and seasonal infections.

In human therapy, the dose proposed for the derivatives of the present invention is approximately between 100 and 300 mg/day, administered for example in the form of tablets, capsules or suppositories.

Hereinafter, by way of example, three particular gallenic forms of the derivatives, the objects of the present invention, will be indicated.

Example of formula per tablet

6-chloro-3-methyl-1, 3-benzoxazine-2, 4-dione	100 mg
Avicel pH—102	100 mg
Primojel	10 mg
Aerosil—200	1 mg
Magnesium stearate	2 mg
Tablet weight	213 mg

Example of formula per capsule

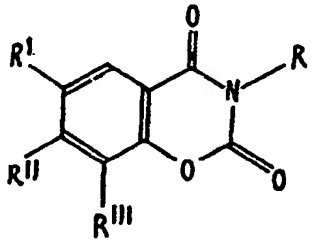
6-chloro-3-methyl-1, 3-benzoxazine-2, 4-dione	100 mg
Lactose	75 mg
Avicel pH—102	25 mg
Aerosil—200	1 mg
Magnesium stearate	2 mg
Capsule weight	203 mg

Example of formula per suppository

6-chloro-3-methyl-1, 3-benzoxazine-2, 4-dione	0.2 g
Monolene	1.8 g
Suppository weight	2.0 g

CLAIMS

1. A derivative of 1,3-benzoxazine-2,4-dione of the general formula



(I)

in which R represents an alkyl radical, an ortho-phenoxy-phenyl, ortho-thiophenoxy-phenyl, a benzyl, furfuryl or 2-pyridyl group; R' represents a hydrogen, chlorine, or bromine atom or a methoxy radical; R'' represents a hydrogen or chlorine atom or a methyl radical; and R''' represents a hydrogen, chlorine or bromine atom.

2. A derivative as claimed in claim 1 wherein R represents a lower alkyl radical.

3. A derivative as claimed in claim 1 wherein R represents an alkyl radical with 1 to 4 carbon atoms.

4. 6-chloro-3-methyl-1, 3-benzoxazine-2, 4-dione.

5. 6-chloro-3-ethyl-1, 3-benzoxazine-2, 4-dione.

6. 6-chloro-3-propyl-1, 3-benzoxazine-2, 4-dione.

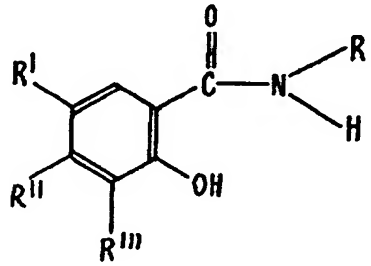
7. 6-chloro-3-furfuryl-1, 3-benzoxazine-2, 4-dione.

8. 6-chloro-3-(o-phenoxyphenyl)-1, 3-benzoxazine-2, 4-dione.

9. 6-chloro-3-(o-thiophenoxylphenyl)-1, 3-benzoxazine-2, 4-dione.

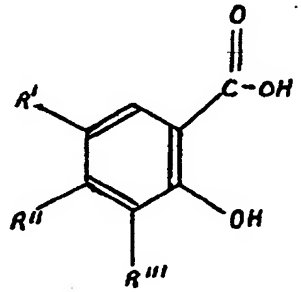
10. 6-bromo-3-methyl-1, 3-benzoxazine-2, 4-dione.

11. A method of preparation of a derivative as claimed in claim 1, wherein a derivative of salicylamide of the general formula



in which R, R', R'' and R''' have the meaning indicated in claim 1 is reacted with ethyl chlorocarbonate.

12. A method of preparation of a derivative as claimed in claim 1, wherein a derivative of salicylic acid of the general formual



in which R', R'' and R''' have the meaning indicated in claim 1, is reacted with an isocyanate of general formula

$$O=C=N-R$$

in which R has the meaning given in claim 1.

13. A method as claimed in claim 14, conducted substantially as described in Example 1.

14. A method as claimed in claim 15, conducted substantially as described in Example 2.

15. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 13 together with a pharmaceutically acceptable carrier.

16. A pharmaceutical composition as claimed in claim 19 in the form of a tablet, capsule or suppository.

17. A pharmaceutical composition as claimed in claim 19 substantially as described in the Examples herein.

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